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Attn: Examiner Lorraine Spector
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FROM: William J. Wood
OUR REF.: G&C 669.23-US-WO
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Applicant:	Audrey Goddard et al.
Serial No.:	09/202,054
Filed:	December 7, 1998
Group Art Unit:	1647
Title:	ANTIBODIES TO HUMAN TOLL HOMOLOGUES
Our Ref. No.:	G&C 669.23-US-WO

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Audrey Goddard et al.	Examiner:	Lorraine Spector
Serial No.:	09/202,054	Group Art Unit:	1647
Filed:	December 7, 1998	Docket:	G&C 669.23-US-WO
Title:	ANTIBODIES TO HUMAN TOLL HOMOLOGUES		

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Commissioner for Patents
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Alexandria, VA 22313-1450

Dear Sir:

We are transmitting herewith the attached:

☒ Transmittal sheet, in duplicate, containing a Certificate of Mailing or Transmission under 37 CFR 1.8.
☒ Reply Brief of Appellant(s).

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Inventor: Audrey Goddard et al.	)	
Examiner: Lorraine Spector, Ph.D.	)	
Serial #: 09/202,054	)	Group Art Unit: 1647
	)	
Filed: December 7, 1998	)	Appeal No.: _____
	)	

Title: ANTIBODIES TO HUMAN TOLL HOMOLOGUES

REPLY BRIEF OF APPELLANTS

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In accordance with 37 CFR §41.37, Appellants hereby submit an Amended Brief on Appeal from the final rejection in the above-identified application, as set forth in the Examiner's Answer dated June 27, 2007

I. STATUS OF CLAIMS

Claims 28-30, 48-50 and 54-57 are pending in the application. In response to the Notification of Non-Compliant Appeal Brief dated December 7, 2006, Appellants' attorney notes that, in accordance with the Examiner's comments, claims 28 and 30 in the Claims Appendix below now correspond to the claims on appeal and of record on July 15, 2004.

Claims 28 and 48 have been rejected under 35 U.S.C. §102(b).

Claims 29, 49, 50 and 54 have been rejected under 35 U.S.C. §103(a).

Claims 28-30, 48-50 and 54-57 have been rejected under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

The rejections of claims 28-30, 48-50 and 54-57 are being appealed.

II. GROUNDS OF REJETION TO BE REVIEWED ON APPEAL

Claims 28 and 48 stand rejected under 35 U.S.C. §102(b) as being anticipated by Ruggeri et al., WO 91/09614 (Ruggeri).

Claims 29 and 49 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ruggeri et al., WO 91/09614 (Ruggeri) in view of Coughlin, United States Patent No. 5,256,766 (Coughlin).

Claims 50 and 54 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ruggeri et al., WO 91/09614 (Ruggeri) in view of Coughlin, United States Patent No. 5,256,766, and further in view of Ladner et al., United States Patent Application No. 4,946,778 (Ladner).

Claims 28-30 and 48-51 stand rejected under 35 U.S.C. §101.

Claims 28-30 and 48-51 stand rejected under 35 U.S.C. §112, first paragraph in view of the rejection under 35 U.S.C. §101.

All of these rejections are being appealed.

III. ARGUMENTS

In this Reply Brief, Appellants review the arguments in the Examiner's Answer that provide the foundation for the rejections under 35 U.S.C. §102, 35 U.S.C. §103, 35 U.S.C. §101 and 35 U.S.C. §112. Appellants then identify how the Patent Office's rejections are contrary to case law that governs the proper application of these statutes.

A. ARGUMENTS TRAVERSING REJECTIONS OF CLAIMS 28, 29, 48, 49, 50 AND 54 UNDER 35 U.S.C. §102(b) OR 35 U.S.C. §103(a)

The Patent Office's rejection of all pending claims under U.S.C. §102(b) or 35 U.S.C. §103(a) requires a conjecture regarding what products might result from the practice of a prior art process, specifically that the procedure for making antibodies using a 15 residue platelet membrane glycoprotein Ib peptide as an immunogen that is described in Ruggeri et al., WO 91/09614 (Ruggeri) might serendipitously produce an antibody that has dual affinity characteristics, namely: (1) an ability to bind the 15 residue platelet membrane glycoprotein Ib peptide; and in addition (2) an ability to bind a PRO285 polypeptide comprising amino acids 1 to 1049 encoded by SEQ ID NO:2 (e.g. Appellants claim 28). In particular, because Ruggeri fails to provide any disclosure relating to the PRO285 gene, much less an antibody that binds a polypeptide encoded by the PRO285 gene, the rejections under U.S.C. §102(b) and 35 U.S.C. §103(a) are predicated on this Patent Office conjecture as to the inherent binding characteristics of an antibody product that might result from the practice of the processes disclosed in the Ruggeri reference. In a specific illustration of this conjecture, the Patent Office asserts for example that "[I]t remains that is it well known in the art to raise antibodies to such peptides as disclosed by Ruggeri, and as taught by Ruggeri, and that among those antibodies, one would expect antibodies within the metes and bounds of the claims" (page 10 of the Examiner's Answer).

Appellants traverse this rejection for the technical reasons noted in the Appeal Brief and further because it is contrary to case law which holds that "anticipation of inventions set forth in product claims **cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references**" (see, e.g. *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 314 (Fed. Cir. 1983), emphasis added). Similarly, while the

Patent Office rejects claims 28 and 48 as anticipated by the Ruggeri disclosure because "**one would expect** antibodies within the metes and bounds of the claims" (page 10 of the Examiner's Answer, emphasis added), case law explicitly holds that anticipation cannot be predicated upon this type of disclosure, i.e. a disclosure where a material element or limitation is "merely probably or possibly present" (see, e.g. *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 63 USPQ2d 1597, 1599 (Fed. Cir. 2002)). Instead, an inherently anticipatory reference "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference" (see, e.g. M.P.E.P. 2112 and *Continental Can Co. v. Monsanto Co.*, 20 USPQ 2d 1746, 1749 (Fed. Cir. 1991)). Because it is clear from the holdings in *W.L. Gore v. Garlock, Inc., Trintec Indus., Inc. v. Top-U.S.A. Corp.* and *Continental Can Co.*, that conjecture respecting characteristics of products (e.g. an expectation of antibodies having dual affinity characteristics) that might result from the practice of processes disclosed in a prior art reference (e.g. immunization with a platelet membrane glycoprotein Ib peptide) cannot serve as the basis for a finding of anticipation, Appellants respectfully request a withdrawal of the rejections under 35 U.S.C. §102(b).

In the Examiner's Answer, the Patent Office maintains it rejection of dependent claims 29 and 49 (which recite monoclonal antibody embodiments of the invention) under 35 U.S.C. §103(a) in view of a combination of the disclosure in Ruggeri with the disclosure relating to monoclonal antibodies in Coughlin (U.S. Patent No. 5,256,766). The Patent Office then combines the disclosures of Ruggeri, Coughlin and Ladner et al. (U.S. Patent No. 4,946,778) to reject dependent claims 50 and 54 (directed to chimeric, humanized or human antibody embodiments of the invention) in view of the teachings relating to single chain antibodies in Ladner et al.

Appellants traverse the rejections under 35 U.S.C. §103(a) because like Ruggeri, neither Coughlin nor Ladner teach or suggest a PRO285 polypeptide comprising amino acids 1 to 1049 encoded by SEQ ID NO:2, much less an isolated antibody that bind to this polypeptide. As noted in MPEP §2142 and 2143.03, in order to establish the obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In this context, because the Coughlin and Ladner disclosures fail to remedy the deficiencies of the Ruggeri disclosure, these references cannot be combined in a manner that produces the antibodies recited in the pending claims. For this reason, Appellants respectfully request a withdrawal of the rejections under 35 U.S.C. §103(a).

B. ARGUMENTS TRAVERSING REJECTIONS OF CLAIMS 28-30, 48-50 AND 54-57 UNDER 35 U.S.C. §101

Applicants' statements of utility are presumed to be true and to overcome the presumption of truth that the application enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e. "question") the truth of the statement of utility. See, e.g. *In re Langer*, 183 USPQ 288 (CCPA 1974) and *In re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992). In its efforts to overcome Appellants' presumption of utility, the Examiner's Answer sets forth a number of erroneous analyses of the data provided in the specification (and cited by the expert witness) as well as the disclosures in various journal articles. As shown below, the Patent Office has not overcome Appellants' presumption of utility because one of skill in the relevant art would not agree with the analyses that are provided by the Patent Office in their efforts to establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of Appellants' statement of utility.

At page 5 of the Examiner's Answer, the Patent Office asserts that an independent homology analysis of the TLR2 and PRO285 polypeptides that was conducted by Patent Office has determined that, contrary to was is taught in Appellants' specification, no significant homology exists between these polypeptides ("when the sequence of PRO285 was searched against all available databases, that no significant homology to TLR2 was detected"). At page 4 and again at page 13 of the Examiner's Answer, the Patent Office then asserts the disclosure in Jurk et al., Nature Immunology 3(6), 499 (2002) teaches that "a synthetic compound with antiviral activity has not been described as a ligand for TLR7" and supports the utility rejection. At page 13 of the Examiner's Answer, the Patent Office then states that the disclosure in the Beutner et al., Am J Med. 1997;102(5A):28-37, a prior art article that is included in the evidence Appendix of the Appeal Brief (cited by Appellants for its teaching of the use of an imidazoquinoline to induce the expression of IL-1, IL-6 and IL-8 in the topical treatment of warts) is unpersuasive because "the terms IL-1, IL-6, IL-8 and, do not appear in any portion of the article". At page 17 of the Examiner's Answer, the Patent Office then relies upon a combination of these analyses to assert that the claimed subject matter lacks a specific, substantial and credible utility, arguing for example that

Patent Office analysis of the disclosure data and teachings in the prior art show that "antibodies to PRO285 would not have been useful to interfere with production of IL-1, 6 or 8 unless such production was induced by PRO285, which is neither predictable nor shown".

Appellants respectfully traverse this rejection because one of skill in the art would not agree with the above-noted arguments that the Patent Office asserts overcome Appellants' legal presumption of utility. For example, while the recent homology search programs and/or set of search parameters employed by the Patent Office apparently failed to identify significant homology between PRO285 and TLR2, Appellants note that their BLAST and FastA sequence alignment analyses (using the ALIGN computer program) of the full length PRO285 sequence did show that it is homologous to TLR2 (see, e.g. page 40, lines 19-23). Moreover, it is undisputed that this homology is significant enough for those of skill in this art to group both of these polypeptides together within the Toll-like receptor family (see, e.g. page 362 of the Du et al. article cited at pages 3 and 17 of the Reply Brief). Consequently, when using properly designed programs and/or sets of search parameters, artisans in this field of technology find that significant homologies between the TLR2 and PRO285 polypeptide sequences do in fact exist (even if they are missed by the Patent Office's independent homology analyses of these polypeptides). For this reason, a skilled artisan would not agree with the Patent Office's assertion that it is not possible to detect significant homology between PRO285 and TLR2.

In response to the Patent Office's characterization of the Jurk disclosure as quoted above, Appellants respond by noting that Jurk does in fact teach that a synthetic imidazoquinoline compound having antiviral activity binds to TLR7/PRO285 and induces the expression of NF-κB (see, e.g. the abstract). For this reason, one of skill in the art would not agree with the Patent Office's characterization of the disclosure in the Jurk article. In response to the Patent Office's assertion that Appellants' reliance on the Beutner article (i.e. as illustrating a nexus between NF-κB signaling, the induction of the IL-1, IL-6, IL-8 cytokines and therapeutic methods) is unpersuasive because for example that the terms IL-1, IL-6, IL-8 do not appear in any portion of the Beutner article, Appellants' attorney directs the Patent Office to the text in the first column of page 34 of Beutner ("Imidiquod also induces a variety of other cytokines in peripheral blood mononuclear cells,

including Interleukin-1 (IL-1), IL-6, IL-8. . .."). For this reason, a skilled artisans would not agree with the Patent Office's characterization of the disclosure in the Beutner article.

For the reasons noted above, one of skill in the art would not agree with the analysis used by the Patent Office to reject the claims under 35 U.S.C. §101. Instead, the skilled artisan would note that Appellants' specification asserts a utility for the claimed subject matter that conforms to well known scientific principles such as comparative homology analyses and functional data from Toll family members which indicate that PRO285 polypeptide signaling activates NF-κB, an event which leads to the expression of the inflammatory cytokines IL-1, IL-6 and IL-8. See, e.g. page 13, lines 13-25. As noted in both the specification (e.g., page 37, lines 10-29) and the Beutner article (e.g. page 34, first column), methods designed to modulate the expression of IL-1, IL-6 and IL-8 are useful in therapeutic methods. Consequently, the utility of the claimed anti-PRO285 antibodies is based for example upon the Appellants' understanding that PRO285 polypeptide signaling modulates NF-κB activity and that antibodies specific for this receptor can modulate this activity. In this context, the claimed subject matter has a credible, specific and substantial utility because the modulation of NF-κB modulates the expression of the inflammatory cytokines IL-1, IL-6 and IL-8; and pathologies such as septic shock and warts are treated via the modulation of IL-1, IL-6 and IL-8 expression.

As noted in M.P.E.P. §2107.02, where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong" even when there may be reason to believe that an assertion is not entirely accurate. Instead, an assertion of utility is to be considered credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. In order to overcome the presumption that an asserted utility is true, Patent Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered "false' by a person of ordinary skill in the art. See, e.g. *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974). In the instant case, the analysis of the disclosure and associated art references provided by the Patent Office to make these rejections fails to do so. Consequently, the presumption that Appellants' statement of utility is true has not been overcome by the various arguments presented by the Patent Office. For these reasons, based upon

the claims and the asserted utility, there are clear errors in the Patent Office's rejection and further, the rejections fail to establish the elements needed for a prima facie rejection under 35 U.S.C. §101. The withdrawal of this rejection is therefore requested.

C. ARGUMENTS TRAVERSING REJECTIONS OF CLAIMS 28-30, 48-50 and 54-57 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

In the Examiner's Answer, the Patent Office asserts the claimed subject matter is both anticipated by Ruggeri (see, e.g. the rejection under 35 U.S.C. §102(b) at page 7) and further that this subject matter is not enabled (see, e.g. the rejection under 35 U.S.C. §112, first paragraph at page 18). In response, Appellants' attorney first notes that the case law regarding 35 U.S.C. §102(b) unambiguously requires an anticipatory disclosure to be enabled (see, e.g. *In re Donohue*, 226 USPQ 619 (Fed. Cir. 1985). Consequently, it is legally impossible for both the anticipation rejection made by the Patent Office and the enablement rejection made by the Patent Office to be correct. In fact, in the instant situation, neither of the legally conflicting arguments made by the Patent Office is correct. The deficiencies in the Patent Office's anticipation rejection were briefly reviewed above. The deficiencies in the Patent Office's enablement rejection are briefly reviewed below.

In the Examiner's Answer, the Patent Office asserts that because the claimed invention is not supported by either a specific, substantial and credible asserted utility, one skilled in the art clearly would not know how to use the claimed invention, and this invention is therefore not enabled (resulting in a rejection under 35 U.S.C. §112, first paragraph). In response, Appellants note that M.P.E.P. §2164.07 states that Office personnel should not impose a 35 U.S.C. §112, first paragraph, rejection grounded on a "lack of utility" basis unless a 35 U.S.C. §101 rejection is proper. As shown in the comments in the sections above, the rejection under 35 U.S.C. §101 rejection is not proper and should be withdrawn. The rejection under 35 U.S.C. §112 that is associated with the rejection under 35 U.S.C. §101 is not proper for the same reasons and should therefore be withdrawn as well.

In the Examiner's Answer, the Patent Office presents new arguments in support of the enablement rejection that were not presented in any previous Office Actions. In particular, at page 19 of the Examiner's Answer, the Patent Office's asserts that a lack of enablement is evident in the

instant case because "despite appellants assertion that PRO285 has "homology" to TLR2, that no significant homology to TLR2 was detected when the sequence was searched by the Examiner". At page 19 of the Examiner's Answer, the Patent Office then states that because their homology analysis demonstrates that it is not possible to detect any significant homology between PRO285 and TLR2, undue experimentation is required to "determine what the properties of PRO285 are, and how to turn such into a use within the meaning of 35 U.S.C. §112, first paragraph".

In responding to the Patent Office's new rationale for the enablement rejection, Appellants point out that there are many different search programs and parameters that artisans use to identify such homologies. In the instant case, the specification teaches that BLAST and FastA sequence alignment analyses (using the ALIGN computer program) of the full length PRO285 sequence show that it is homologous to TLR2 (see, e.g. page 40, lines 19-23). In this context, Appellants' attorney does not know why whatever computer programs used and/or search parameters employed by the Patent Office in their independent homology analysis failed to identify the homologies identified by Appellants' BLAST and FastA sequence alignment analyses as disclosed in the specification. However, Appellants do note that the disclosures in the Jurk et al., and Du et al. articles that are cited at page 3 of the Examiner's Answer both show that artisans can readily identify those search parameters that do allow them to identify a homology between PRO285 and TLR2, a homology that is significant enough to classify both of these polypeptides as within the Toll-like receptor family (see, e.g. page 362 of the Du et al.). Consequently, one of skill in the art would not agree that the Patent Office's recent inability to detect any significant homology between PRO285 and TLR2 provides probative evidence that the instant invention is not enabled.

35 U.S.C. §112 requires that, in viewing the evidence as a whole, one skilled in the art would believe that the claimed invention can be made and used with a reasonable expectation of success (see, e.g. *In re Robins*, 166 USPQ 552, 556, CCPA 1970). As shown for example by the comments provided above as well as the declaration under 37 C.F.R. 1.132 that was submitted with the office action response on December 9, 2003, one skilled in the art would not doubt the asserted utility and would know how to use the claimed invention without undue experimentation. For these reasons, there are clear errors in the Patent Office's enablement rejection. For this reason, Appellants respectfully request a withdrawal of the rejection under 35 U.S.C. §112.

IV. CONCLUSION

In light of the above arguments, Appellants respectfully submit that the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §103(a) are in error because the references cited by the Patent Office neither anticipate nor render obvious the claimed invention. In addition, Appellants respectfully submit that the rejections under 35 U.S.C. §101 and 35 U.S.C. §112 are in error because the Patent Office fails to provide evidence sufficient to show that the statement of asserted utility would be considered "false' by a person of ordinary skill in the art. As a result, a decision by the Board of Patent Appeals and Interferences reversing these rejections and directing allowance of the pending claims in the subject application is respectfully solicited.

Respectfully submitted,

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